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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,292	GALEN, JAMES E.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1 and 2*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The response and amendment filed 1-15-04 has been entered into the record. Claims 1-7 are pending and under examination. Claims 8-20 have been canceled.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-7 of this application. In particular the provisional document fails to provide written description for use of the nucleic acid encoding SEQ ID NO:2 (clyA) from *Salmonella enterica* serovar typhi, the clyA gene from *S. paratyphi*, the clyA gene from *Escherichia coli* and as such does not enable the scope of the instantly claimed invention as is claimed herein.

Information Disclosure Statements

The information disclosure statement filed July 25, 2002 has been considered in part. The information disclosure statement filed July 25, 2002, is missing the non-patent literature and as such the disclosure statement has been considered with respect to the Patent Literature only at this time. A replacement copy of the missing non-patent literature references is requested for consideration of these references and to complete the electronic record.

The information disclosure statement filed May 21, 2003 has been considered and an initialed copy is enclosed.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, or

they are present on an information disclosure statement filed by Applicants, they have not been considered.

Specification

The attempt to incorporate subject matter into this application by reference to GenBank nucleic acid sequences is improper because this material is esssential for the description of the genes and proteins used in the claimed method. The sequences in GenBank are subject to changes and are not immutable in time and as such, this incorporation by reference is improper becuase it relies upon essential material not set forth in the specificaiton that is required to practice the claimed invention. Applicants are directed to In re Hawkins

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing a fusion protein comprising a

clyA protein of Salmonella enterica serovar Typhi fused to a protein of interest in *Salmonella enterica* serovar Typhi comprising providing an expression vector to a population of untransformed *Salmonella enterica* serovar Typhi cells to produce a population of transformed *Salmonella enterica* serovar Typhi wherein the expression vector comprises an expression cassette comprising SEQ ID NO:2 operatively linked 5' to the gene encoding the protein of interest and cultivating transformed *Salmonella enterica* serovar Typhi in a bacterial medium and expressing the expression cassette to produce the fusion protein wherein the fusion polypeptide is exported from *Salmonella enterica* serovar Typhi into the bacterial medium, it does not reasonably provide enablement for methods using other clyA genes or use of any bacterial cell in combination with any clyA gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The teaching of the specification are limited to an expression vector comprising an expression cassette comprising SEQ ID NO:2 operatively linked 5' to the gene encoding the fluorescent reporter green fluorescent protein or sacB and cultivating transformed *Salmonella enterica* serovar Typhi in a bacterial medium and expressing the expression cassette to produce the fusion protein wherein the fusion polypeptide is exported from *Salmonella enterica* serovar Typhi into the bacterial medium. The claims are drawn to a fusion protein of any export protein sequence with any gene of interest in combination with any bacterial host cell. The claims are further limited to undefined clyA genes as the export protein sequence in combination with any bacterial cell and finally SEQ ID NO:2 or specific mutants thereof in combination with any bacterial cell.

The teachings of the art with respect to SEQ ID NO:2 and cytolysin A (clyA) genes and how these cytolysins are exported in general is very limited. In contrast to other secretory systems in bacteria, the mode of export of the polypeptides designated herein as clyA in bacterial cells is unknown to the art and undocumented by the specification.

The interchangeability of one species clyA with any other species of clyA protein for export purposes in heterologous bacterial cells is unknown and undocumented by the teachings of the specification and the art. Many protein transport systems that export directed proteins use associated proteins that are required for the functional export of the cytolysin/hemolysin such as type I secretion systems in *E. coli* (hlyA) and sec-dependent secretion systems in *E. coli*. Since the secretion machinery that enables the clyA protein to be exported is completely unknown to the art and the teachings of the specification are limited to fusions comprising SEQ ID NO:2 (the clyA of *Salmonella enterica* serovar Typhi) and their production in its homologous bacterium (*Salmonella enterica* serovar Typhi), it is not clear if the clyA transport machinery can utilize variants of clyA as claimed or can recognize/transport heterologous clyA proteins or fusions comprising these cytolysins. The specification fails to teach that a mutant clyA protein is functionally exported such that one skilled in the art would reasonably expect that a fusion protein comprising such would be exported. The ability of any of the recited mutations to attenuate hemolytic activity is undocumented by the specification and the effect on one or even a combination of the mutations with respect to hemolytic activity of the protein from which it is derived is undocumented by the specification or the art. The art teaches that similar cytolysins/hemolysins such as slyA is not secreted in heterologous cells. Goebel et al, US. Patent 5,525,504 teaches that functional salmolysin recombinantly expressed in *E. coli* was recovered by release from the *E. coli* by osmotic shock and as such the salmolysin was not secreted in a heterologous host. Therefore, in the absence of specific teaching in the specification to the contrary, one skilled in the art would have reason to doubt that the cytolysin would be secreted in heterologous host cells or that mutations at the claimed positions result in decreased hemolytic activity as claimed. Further, there are many different proteins that have cytolytic and hemolytic activity from the family of *Enterobacteriaceae* and the recitation of "clyA" does not structurally distinguish one hemolysin from another. This problem is recognized in the specification

where there are at least three designations for the same cytolysin/hemolysin in E. coli (ClyA, HlyE and SheA). As such, the recitation of clyA does not confer a specific structure on the gene or protein used and in the absence of a 100% sequence identity as compared with SEQ ID NO:2, it is not clear that the proteins related by homology possess the same functional characteristics as SEQ ID NO:2 (the clyA from S. Typhi). Absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981 (1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)]. In particular Attwood (Science, 290:471-473, 2000) teaches that "... it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences (and it is not always clear what we mean by "function"); very few structure are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently teach function); the degree of

automation that has been used of necessity with its imperfect tools and protocols, has led to the accumulation of much database misinformation...". The recited genes lack evidentiary support of functional secretion and the biological activity of cytolysis/hemolysis at the time of filing.

Therefore, in the absence of further guidance from Applicants as to the points set forth above, in view of the unpredictability of the art, it would require undue experimentation to make and use the invention commensurate in scope with the instantly claimed invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 1 and every claim dependent thereon (claims 2-7) the claims are indefinite because the term "the culture medium" lacks antecedent basis in the claim. Further, the claim is technically incorrect since an expression vector is a nucleic acid sequence and can not contain an export coding sequence genetically fused to a protein of interest. While the expression vector can comprise a nucleic acid sequence encoding a fusion protein wherein the fusion protein comprises a export protein sequence fused to a protein of interest, it can not fuse a nucleic acid sequence to a protein sequence as is currently recited.

As to claim 2, the actual bacterial cell employed unclear since it uses terminology inconsistent with the correct taxonomic designation or that commonly used in the art. While Applicants can be their own lexicographer, the employed abbreviation can not cause confusion regarding the metes and bounds of the claim. Correction is required.

As to claim 4, while the claims can use abbreviations or acronyms such as "clyA", the claims must first provide the entirety of the term followed by the acronym, so that

there is no confusion as to the meaning of such an abbreviation/acronym. Correction is required.

Claim Rejections - 35 USC § 102 or 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the

applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Ikonomidis et al (J.Exp. Med. 180:2209-2218, 1994).

The claims are drawn to a method of expressing a gene in a bacterial cell comprising providing an expression vector to a population of untransformed bacterial cells wherein the expression vector comprises an expression cassette comprising a sequence encoding an export protein sequence genetically fused to a antigen/antigen of interest.

Ikonomidis et al teach the stable expression and extracellular secretion of a fusion protien comprising listeriolysin O (LLO) and nucleoprotein (NP) called LLO-NP. Ikonomidis et al teach an expression vector encoding the fusion protien LLO-NP and its expression and secretion when expressed in *Listeria monocytogenes* (see page 2212, column 2, Results, *Construction of L. monocytogenes Strains Secreting NP.*) Because both the LLO of the art and the clyA of the claims have the same function (lysis of cells) and that the structure of the genes are not specified in the claim, the LLO of the prior art meets the limitation of clyA of the claims since they both have lytic activity and are secreted and as such the term clyA does not structurally or functionally distinguish one lysin from another.

Claims 1, 3, 4, and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Gentschev et al (Behring Inst Mitt, 98:103-113, 1997; of record in 1449).

The claims are drawn to a method of expressing a gene in a bacterial cell comprising providing an expression vector to a population of untransformed bacterial cells wherein the expression vector comprises an expression cassette comprising a sequence encoding an export protein sequence genetically fused to a antigen/antigen of interest. The claims are

further limited to a bacteria cell is an *E. coli* or clyA genes from *Salmonella* sp. or *E. coli* that lack a specific defined structure.

Gentschev et al teach that the *E. coli* hemolysin hlyA secretion apparatus is fully functional in *Salmonella*. Gentschev et al teach an expression vector that provides for secretion of a HlyAs fusion protein (see page 105, column 1 to page 106, column 2). Fusion protiens comprising the nucleic acid sequence of hlyA linked 3' to an protein of interest (*Listeria* antigens) are effeciently secreted from bacterial cells in *E. coli*, *Salmonella typhimurium* and *S. dublin*. Gentschev et al teach construction of *Salmonella* strains which secrete antigens fused to hlyAs (see page 107, column 2 to page 108, column 2) are effeciently secreted (Figure 1). Gentschev et al also teach that the genetic information for antigen of any source ranging in size between 10 and 1000 amino acids can be easily inserted into the secretion vector which will allow the secretion of fused antigens in attenuated *Salmonella typhimurium* strains and in other attenuated *Enterobactericeae*. Because both the hylA of the art and the clyA of the claims have the same function (lysis of cells) and that the structure of the genes are not specified in the claim, the hlyA of the prior art meets the limitation of clyA of the claims since they both have hemolysin activity.

Claims 1-4 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gentschev et al (Behring Inst Mitt, 98:103-113, 1997) in view of Curtis, III et al (U.S. Patent No. 5,387,744 issued February 7, 1995; of record in 1449).

Gentschev et al (Behring Inst Mitt, 98:103-113, 1997) is set forth *supra*. Gentschev et al differ by not teaching the expression of the fusion antigen in *Salmonella typhi* or *Salmonella enterica* serovar typhi. However, Gentschev et al teaches that the genetic information for antigen of any source ranging in size between 10 and 1000 amino acids can be easily inserted into the secretion vector which will allow the secretion of

fused antigens in attenuated *Salmonella typhimurium* strains and in other attenuated *Enterobactericeae*.

Curtis, III et al teach avirulent (i.e. attenuated) derivatives of *S. Typhi* having attenuated mutations of the *cya* and/or *crp* and/or *cdt* genes.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the *S. Typhi* of Curtis, III et al for the *E. coli*, *Salmonella typhimurium* or *Salmonella dublin* for construction of attenuated *Salmonella* strains which secrete antigens fused to HlyAs because Gentschev et al teaches that the genetic information for antigen of any source ranging in size between 10 and 1000 amino acids can be easily inserted into the secretion vector which will allow the secretion of fused antigens in attenuated *Salmonella typhimurium* strains and in other attenuated *Enterobactericeae* and the avirulent *S. Typhi* of Curtis III, et al is another *Salmonella* specie that belongs in the family of *Enterobacteriaceae*.

Status of the Claims

All claims stand rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 703-305-7555. After January 27, 2004 the examiner can be reached at telephone number 571-272-0855 The examiner can normally be reached on M-F 9:30pm-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Smith Lynette can be reached on before January 27, 2004 at 703-308-3909, after January 27, 2004 at 571-272-0864. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645